I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on October 13, 2010.

Frank C. Eisenschenk, Ph.D., Patent Attorney

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 CFR 1.322 AND UNDER 37 CFR 1.323
Docket No. INN.135

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Christian Belmant, Patrice Nury
Issued	:	August 3, 2010
Patent No.	:	7,767,842
Conf. No.	:	1963
For	:	Class of Gamma Delta T Cells Activators and Use Thereof

Mail Stop Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION
UNDER 37 CFR 1.322 (OFFICE MISTAKE) AND
UNDER 37 CFR 1.323 (APPLICANT MISTAKE)

Sir:

A Certificate of Correction for the above-identified patent has been prepared and is attached hereto.

In the left-hand column below is the column and line number where errors occurred in the patent. In the right-hand column is the page and line number in the application where the correct information appears or should appear.

Patent Reads:	**Application Reads:**
Column 2, line 36:	Page 2, lines 28-29:
"circulating 75 T cells"	--circulating γδ T cells--

J:\INN\135\PTO-Misc\COC.Req.doc/DNB/knm

Patent Reads:

Column 3, line 15:

"that other compounds"

Column 5, line 54:

"inventions provides"

Column 7, lines 56-57:

"increased in potency"

Application Should Read:

Page 3, line 24:

--than other compounds--

Page 6, line 24:

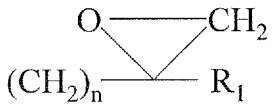
--invention provides--

Page 9, line 16:

--increased potency--

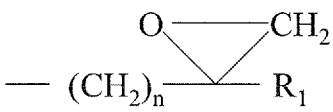
Patent Reads:

Column 11, line 50:

"  "

Application Reads:

Page 14, line 22:

--  --

Patent Reads:

Column 12, line 11:

"can also be targeting"

Column 26, line 28:

"In other aspect"

Column 27, line 54:

"are simultaneously"

Column 27, line 55:

"are sequentially"

Application Should Read:

Page 15, line 9:

--can also be a targeting--

Page 33, line 10:

--In another aspect--

Page 35, lines 5-6:

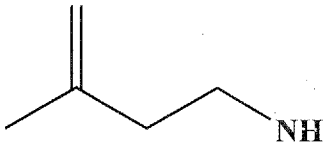
--are simultaneously administered--

Page 35, line 7:

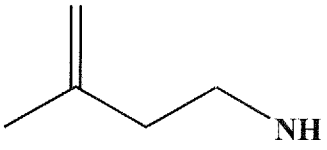
--are sequentially administered--

Patent Reads:

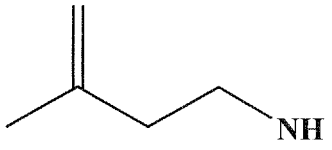
Column 32, line 40:

"  "

Column 34, line 17:

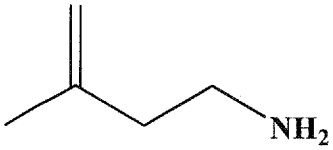
"  "

Column 34, line 60:

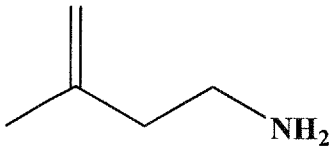
"  "

Application Reads:

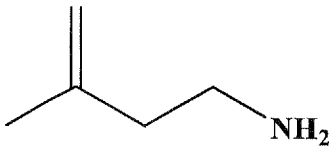
Page 41, line 10:

--  --

Page 42, line 7:

--  --

Page 43, line 3:

--  --.

A true and correct copy of pages 2, 14 and 41-43 of the specification as filed which support Applicants' assertion of the errors on the part of the Patent Office accompanies this Certificate of Correction.

The fee of $100.00 was paid at the time this Request was filed. The Commissioner is also authorized to charge any additional fees as required under 37 CFR 1.20(a) to Deposit Account No. 19-0065.

Approval of the Certificate of Correction is respectfully requested.

Respectfully submitted,

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FCE/knm

Attachments: Copy of pages 2, 14 and 41-43 of the specification

presentation by CD1 or MHC molecules is involved, Vγ9/Vδ2 $^{+}$ lymphocyte activation by non-peptide antigens appears to require cell-to-cell contact (Lang, 1995 ; Morita, 1995 ; Miyagawa, 2001 , Rojas, 2002).

The stimulating bacterial antigens have been shown to be small non peptidic compounds classically referred to as phosphoantigens (Behr et al., 1996; Belmant et al., 2000; Constant et al., 1994; Poquet et al., 1998; Tanaka et al., 1995), owing to the presence of phosphate groups in most instances.

Vγ9/Vδ2 T cells can also be activated through endogenous metabolites (acting in the micromolar range) such as isopentenyl pyrophosphate or IPP (Espinosa et al., 2001b; Tanaka et al., 1995), which is produced through the conventional mevalonate pathway shared by both microorganisms and mammalian cells. Production of IPP in the latter cells can be up-regulated in situations of cell stress and transformation. In particular a recent study has reported a correlation between the endogenous production levels of IPP in tumor cells and their susceptibility to Vγ9/Vδ2 T cell-mediated lysis (Gober et al., 2003).

Also consistent with a direct contribution of endogenous metabolites of the mevalonate pathway to Vγ9/Vδ2 T cell recognition, cell treatment with pharmacological agents preventing IPP biosynthesis (such as statins) or leading to IPP accumulation (such as aminobisphosphonates, see below) lead respectively to decreased or enhanced Vγ9/Vδ2 T cell stimulating properties of the treated cells (Gober et al., 2003; Kato et al., 2001).

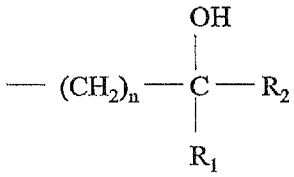
Aminobisphosphonates are thought to inhibit FPP synthase, an enzyme in the mevalonate pathway, the inhibition of which causes the accumulation and release of upstream isoprenoid lipids such as IPP. Aminobisphosphonate compounds had been used in human therapy for the treatment of bone metastases in cancer patients, and provided a first set of evidence for in vivo expansion of human Vγ9/Vδ2 $^{+}$ lymphocytes induced by phosphoantigen agonists, reporting increases of circulating γδ T cells within one to three weeks in human adults with multiple myeloma after therapeutic intravenous injection of 60-90 mg of pamidronate (Kunzmann et al, 1999). However, such compounds require presentation by antigen presenting cells and cannot produce substantial stimulation of Vγ9/Vδ2 T cell activity as assessed by cytokine secretion in a pure Vγ9/Vδ2 T cell culture. Moreover, pamidronate shows very low potency of activation of γδ T cells, reported to achieve at best only 2-fold increase in γδ T cell count (Wilhelm et al., 2003).

trans isoform (E). In a most preferred embodiment, the alkylenyl group is the (E)-4-hydroxy-3-methyl-2-butenyl. In an other preferred embodiment, the alkylenyl group group is an isopentenyl, an dimethylallyl or an hydroxydimethylallyl.

In an additional embodiment, the hydrocarbon group is an alkyl group substituted by an acyl. More preferably, the hydrocarbon group is an (C_4-C_7)alkyl group substituted by an (C_1-C_3)acyl.

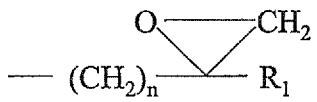
In a further preferred embodiment, R is selected from the group consisting of :

1)



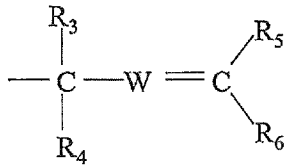
wherein n is an integer from 2 to 20, R_1 is a (C_1-C_3)alkyl group, and R_2 is an halogenated (C_1-C_3)alkyl, a (C_1-C_3)alkoxy-(C_1-C_3)alkyl, an halogenated (C_2-C_3)acyl or a (C_1-C_3)alkoxy-(C_2-C_3)acyl. Preferably, R_1 is a methyl or ethyl group, and R_2 is an halogenated methyl (–CH_2-X, X being an halogen), an halogenated (C_2-C_3)acetyl, or (C_1-C_3)alkoxy- acetyl. The halogenated methyl or acetyl can be mono-, di-, or tri-halogenated. Preferably, n is an integer from 2 to 10, or from 2 to 5. In a more preferred embodiment, n is 2. In a most preferred embodiment, n is 2, R_1 is a methyl and R_2 is an halogenated methyl, more preferably a monohalogenated methyl, still more preferably a bromide methyl. In a particularly preferred embodiment, n is 2, R_1 is a methyl, R2 is a methyl bromide. In a most preferred embodiment, R is 3-(bromomethyl)-3-butanol-1-yl.

2)

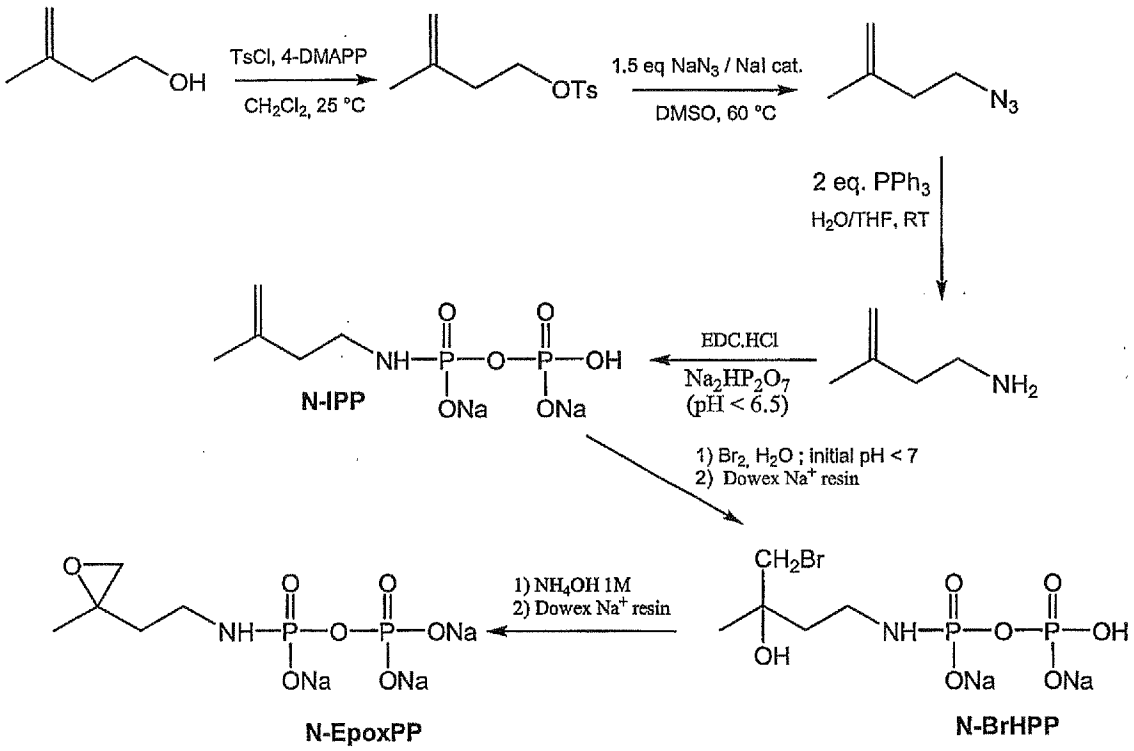


wherein n is an integer from 2 to 20, and R_1 is a methyl or ethyl group. Preferably, n is an integer from 2 to 10, or from 2 to 5. In a more preferred embodiment, n is 2 and R1 is a methyl.

3)



The synthesis of N-IPP, 5-bromo-4-hydroxy-4-methylpentyl pyrophosphoramidate (N-BrHPP) (Example 3) and N-EpoxPP (Example 4) are carried out according to the scheme below. For each step of this synthetic scheme the following references may be used for further guidance: Step 1: Davisson et al., J. Org. Chem., 1986, 51, p 4768-4779; Step 2: Grieco et al, *Tetrahedron* 1986, *42* (*11*), 2847-2853, and Sahasrabudhe, K. et al., *J. Am. Chem. Soc.* 2003; *125*(26); 7914-7922; Step 3: Brettle R. et al., *Bioorg. Med. Chem. Lett.*, vol. 6, p291 (1996); Step 4: Sato et al, *Chem. Pharm. Bull*, 38(8), 2287-2289 (1990); Step 5 : Espinosa, et al, (2001a) J Biol Chem *276*, 18337-18344; and Step 6 : International Patent publication no. WO 00/012519.

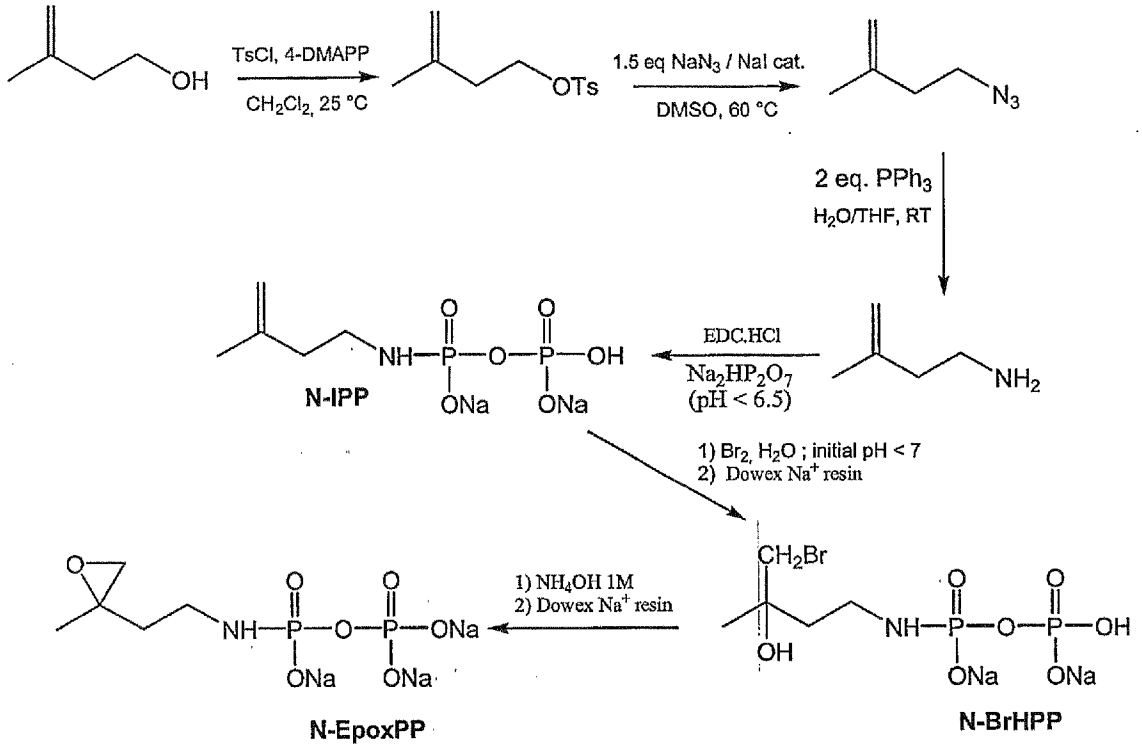


Example 3

Production of 5-bromo-4-hydroxy-4-methylpentyl pyrophosphoramidate (N-BrHPP)

As illustrated in the synthesis scheme below, the compound N-BrHPP can be prepared starting from the compound N-IPP described in Example 2 by addition of bromine water to the alkene function followed by a neutralization on DOWEX 50WX8-200 (Na^+ form) resin. The formation of

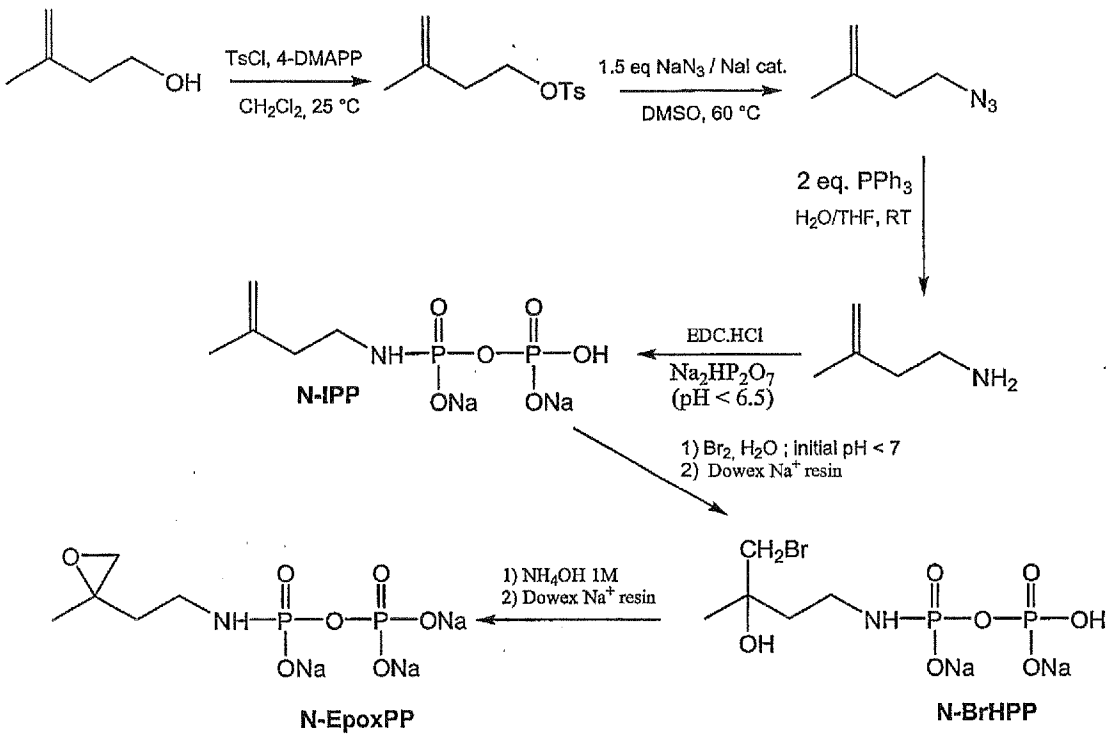
the bromohydrin function with subsequent purification of the crude product can be conducted according to the experimental protocol provided in WO 00/012516 for the preparation of 3-(bromomethyl)-3-butanol-1-yl disphosphate. (BrHPP) or as described in Espinosa et al, *J Biol Chem, 276*, (2001) 18337-18344.



Example 4

Production of 2-(2-methyloxiran-2-yl)ethyl pyrophosphoramidate (N-EpoxPP)

As illustrated in the synthesis scheme below, the compound N-EpoxPP can be prepared starting from the compound N-BrHPP described in Example 3 by treatment with 1M ammonium hydroxide solution (epoxidation reaction) followed by a cationic exchange step on DOWEX 50WX8-200 (Na^+ form) resin. The epoxidation reaction with subsequent purification of the crude product can be conducted according to the experimental protocol provided in WO 00/012519 for the preparation of 3,4-epoxy-3-methyl-1-butyl-diphosphate (EpoxPP).



Example 5

In vitro and in vivo dosage response for N-HDMAPP compound

Cytokine release assay

Cells (primary polyclonal human Vγ9Vδ2 T cells which have been expanded *in vitro* and stored frozen at day 12-15 of expansion) are thawed and rinsed twice and centrifuged. Upon elimination of supernatant and resuspension of cells, the cells are incubated for 24h at 37°C in the presence of IL2 100 IU/ml (final concentration). The cells are washed and centrifuged, following which the supernatant is eliminated and the cells are resuspended and adjusted to the adequate final concentration. The cells are added to the wells of a 96-well plate.

To one row of wells is added a standard dilution series of 3-(bromomethyl)-3-butanol-1-yl-diphosphate (BrHPP). Compounds to be tested, in this case (E)-4-hydroxy-3-methyl-2-butenyl pyrophosphate (HDMAPP) and the N-HDMAPP compound of the invention are added to experimental wells, after several dilutions.

Full plates are incubated 24 hours at 37°C for stimulation of the γδ cells with the test compound and reference compounds, in this case N-HDMAPP, BrHPP and HDMAPP, as further described

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,767,842

APPLICATION NO.: 10/581,144

DATED : August 3, 2010

INVENTORS : Christian Belmant, Patrice Nury

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

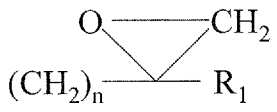
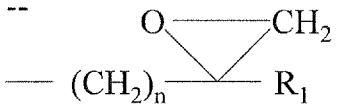
Column 2,
Line 36, "circulating 75 T cells" should read --circulating γδ T cells--.

Column 3,
Line 15, "that other compounds" should read --than other compounds--.

Column 5,
Line 54, "inventions provides" should read --invention provides--.

Column 7,
Lines 56-57, "increased in potency" should read --increased potency--.

Column 11,
Line 50,

"  " should read --  --.

Column 12,
Line 11, "can also be targeting" should read --can also be a targeting--.

MAILING ADDRESS OF SENDER:
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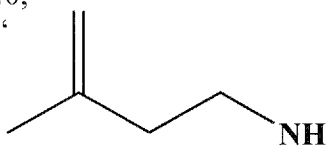
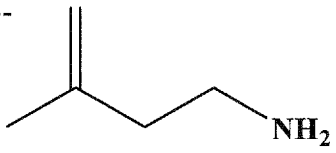
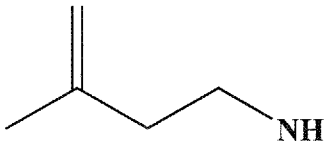
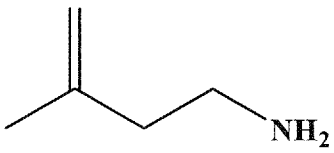
Column 26,
Line 28, "In other aspect" should read --In another aspect--.

Column 27,
Line 54, "are simultaneously" should read --are simultaneously administered--.
Line 55, "are sequentially" should read --are sequentially administered--.

Column 32,
Line 40,

"  " should read --  --.

Column 34,
Line 17,

"  " should read --  --.

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INVENTORS : Christian Belmant, Patrice Nury

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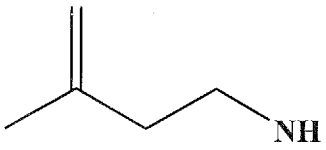
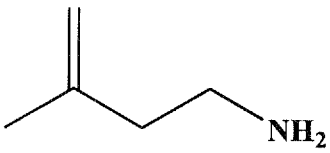
Column 34,
Line 60,

"  " should read --  --.

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